

## Feedback from EAPS, Barcelona , October 2014

### Please give details of the best lecture/learning from the meeting:

#### **1. Prof Kate Costeloe: Results from the Probiotics in Preterms (PIPS) Trial:**

- Multicentre double blind randomised, placebo controlled trial carried out in 1310 infants in the UK. Intervention was a single probiotic strain (*Bifidobacterium breve* BBG-001), administered daily to infants below 31 weeks gestational age.
- No effect of the intervention on any of the primary outcomes (NEC, late onset sepsis or death).
- No adverse effects of the intervention.
- There is no evidence of benefit for preterm infants in routine administration of the probiotic strain tested, in contemporary neonatal practice as carried out in England.
- This study result runs counter to the conclusions of several systematic reviews and meta-analyses that support routine administration of probiotics in preterm infants.
- There are several important distinctions between this trial and other previous trials: PIPS administered the probiotic strain early (<48 hours) and before the infant was enterally fed, and cross contamination was specifically tested for (and was about 40% in the control group).
- The results highlight the importance of large, robustly designed clinical trials that are powered to detect differences in clinically meaningful outcomes (such as death/NEC).
- This trial also asks whether there are strain specific effects of different probiotics and whether, given the large number of available probiotics, whether a different approach is required to determine the efficacy of these alternate strains – possibly demonstrating efficacy in preclinical models prior to the next large RCT.

The bottom line for me is that both PIPS and PROPREAMS (which between them included about 2500 babies) do not show any reduction in death, sepsis or NEC in infants below 28 weeks GA.

**2. Colin Morley speaking about 'How to stabilise the extremely preterm baby'**. Clear evidence based information that is applicable in all healthcare settings and combines scientific enquiry and good quality research, acknowledging the practicalities of management 'on the ground'. Proof that mask inflation technique needs to be learned and demonstrated to be an acquired skill. Subjectiveness of assessment of cyanosis without saturation monitoring. Excellent use of video recording of resuscitation in training and teaching.

**3.** I found the talks on the big data studies and the HFOV masterclass the most useful.

Peter Brocklehurst gave us an overview about the hazards and difficulties in performing large clinical trials and the importance of publishing negative data. Meta-analysis can show a favourable outcome for e.g. IVIG vs placebo meta-analysis favoured decreased mortality but by doing the INIS trial it should be that IVIG did not decrease mortality.

The outcome measure for a trial is so important as highlighted by Prof Brocklehurst e.g. in the ORACLE trial if the gestation at delivery was the primary outcome the trial would have been much smaller and Coamoxiclav would be used for treating women presenting with preterm labour and

PROM and we would have not known that there is an increased incidence of NEC with Coamoxiclav and that Coamoxiclav did not improve outcome in babies i.e. CLD and death and neurodisability.

The BOOST II study is fascinating and it shows the advantage of actually doing a large clinical trial, doing interim analysis and then repeating the study. There was an increased incidence of death in the lower saturation group with no difference in the long term neurodisability. Hence we should target at saturations at 90-95 % and above in preterm infants.

Dr Van Kempen discussed about expectant and intensive treatment for hypoglycaemia and found no difference in the long term outcome in the high risk group.

Prof Costeloe spoke about the PIPS trial and that using a single strain of bifidobacterium was not associated with any advantage. Also different probiotics are used and combining these trials is probably not appropriate.

#### 4. ESPR gives a depth of opportunity for neonatal learning better than any other European meeting.

It is difficult to summarise the key points and best lectures briefly.

- Professor P Brocklehurst's lecture on "Hazards in Planning and Performing Large Perinatal Trials" was an excellent overview. As suggested in the title the challenges of such trials were described with specific reference to many of the large trials he has been involved in including INIS, ORACLE and BOOST II. The importance of unanticipated effects in trials and how these are managed (with reference to the ORACLE Trial) was extremely informative.
- The presentation of the BOOST-II long term data and PiPs outcome data in the same session were excellent with new information available from these trials. The challenges of 2 year follow up in BOOST-II were interesting to hear and applicable to many other current and future trials.
- The Pulmonary Symposium with particular reference to pulmonary hypertension in pre-term infants was an excellent overview of the physiology, evidence and current practice on the subject.
- Several interesting lectures/sessions covering nutrition in the pre-term infant particularly around fortification of MBM and use of DEBM. No new personal learning but thought provoking in terms of local practice and how we might progress care in our local unit.
- Presentation of the results of the "NEUROSIS" study. A multi-centre European (not UK) study of the use of early inhaled Budesonide in the prevention of BPD. Well designed, double blind, multi centre RCT with 850 infants recruited. Study did show some positive benefits but no significant difference in the composite primary outcome. Longer term developmental outcome is awaited.

**Please list 3 key points from the meeting to be shared with the neonatal community:**

1) **Cheryl Battersby, Imperial College; Incidence of NEC in the UK, results from the UK Neonatal Collaborative NEC study:** Using routinely collected clinical data (with case verification by the local clinical team), the incidence of severe NEC (from surgery, histology or post-mortem confirmed cases) was determined among infants 23 to 32 weeks gestation admitted to 80% of all neonatal units in England, in 2012 and 2013. Among 14,294 infants there were 425 cases of severe NEC. The incidence by gestation age was 9.9% for 23-25+6 weeks, 4.5% 26-28+6 weeks. The median postnatal age at NEC surgery was 28 weeks for infants 23-25+6 weeks GA and 30 weeks for infants 26-28+6 weeks GA. About 1/3 babies who require surgery for NEC will die. Interestingly 50% of babies who have severe NEC only ever received breast milk.

2) **Colin Morgan, Liverpool: Insulin treatment for hyperglycaemia, results from the SCAMP trial:** SCAMP was a randomised controlled trial comparing high nutrient PN with standard PN (results previously published in *Pediatrics*). Results presented here were from a post-hoc analysis looking at treatment of hyperglycaemia. Babies were treated with insulin according to a protocol based on blood glucose measurements. Slightly more babies in the high nutrient PN group received insulin treatment (but this was not significant). But when babies were analysed according to whether they received insulin or not (so a non-randomised, post-hoc comparison), babies in the high nutrient arm who received insulin had significantly better head growth than babies that did not receive insulin. This data is pretty speculative but suggests a need for further research into how best to treat hyperglycaemia among preterm babies receiving PN in the first few weeks.

3) **Peter Brocklehurst, UCL: Perinatal clinical trials:** Prof Brocklehurst spoke about how small clinical trials can be misleading, citing the results from the INIS trial as an example. Highlighted the importance of high quality trial design (poor masking or allocation concealment can lead to overestimation of treatment effect by up to 40%, and the importance of using substantive rather than surrogate outcomes. These points seem especially relevant in light of the seemingly conflicting results of the PIPS trial and the numerous systematic reviews and meta-analyses published on probiotics.

1) 2 recent large European studies have shown no association between NEC and Blood transfusion. NEC peak incidence is around 29-32 weeks regardless of gestation, therefore carefully continue to monitor high risk babies, some of whom may be in the nursery. j.neuG. Gainesville Florida

2) PIPs trial showed no benefit for babies given probiotics in any of the outcomes measured, and use of probiotics should remain experimental. Neena Modi

3) Hypothermia slows peak in crp rise by 12 -24 hours, to be aware particularly in cooled patients. E Molloy Trinity college Dublin

1) Target Saturations in preterm neonates at 90-95%. Expect to see slight increase in ROP but lower mortality.

2) Probiotics do not seem to have any advantage in decreasing NEC, LOS and death.

3) Expectant treatment for hypoglycaemia is probably ok for most babies

1) There may be a place for iNO in pre-term infants where there has been oligohydramnios

2) There have been idiosyncratic, pulmonary hypertensive crises described in pre-term infants given Ibuprofen

3) Expectant management (in the Netherlands) of “well” infants at risk of hypoglycaemia (>2kg, >35 weeks) results in the same neurodevelopmental outcome (at 18 months) compared to a more intensive treatment regime